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Of mice, men, and NLGN4

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Editor's Choice Summary

Issue date: (we will complete)

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Volume: (we will complete)

E-locator: (we will complete)

Overline: Autism Spectrum Disorder

Title: Of mice, men, and *NLGN4*

One-sentence summary: Expression of the autism risk factor *NLGN4* is divergent between human and mouse neurons.

Your name: Emily K. Osterweil

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Text of summary

Genetically modified mouse models are of clear value for teasing apart the mechanisms contributing to altered brain function in Autism Spectrum Disorder (ASD). One drawback is that the gene of interest may be functionally divergent in humans. This issue is highlighted in a recent study by Marro et al., which investigates the expression and function of the highly penetrant ASD gene *NLGN4* in human embryonic stem cell (hESC)-derived neurons. The role of the neuroligin-4 protein encoded by *NLGN4* has been described based on studies of the mouse ortholog *Nlgn4*, which is poorly conserved. These studies indicated that neuroligin-4 is modestly expressed in brainstem, retina, and spinal cord, where it is restricted to inhibitory neurons. In contrast, Marro et al. found that neuroligin-4 is highly expressed in post-mortem samples of human cortex and is concentrated in excitatory synapses. They went on to show that overexpression of a mutant *NLGN4* with the R704C mutation identified in ASD increases both excitatory synapse number and excitatory transmission in hESC-derived neurons. In contrast to previous studies of neuroligin-4 in mice, these results suggest that *NLGN4* mutations may contribute to pathophysiology in humans through enhanced rather than diminished excitatory drive.

This work illustrates the importance of investigating disease-relevant mutations in human cellular systems, especially with respect to poorly conserved genes such as *NLGN4*. Now researchers can investigate the extent to which other *NLGN4* mutations disrupt synaptic function in human neurons and test potential therapeutic strategies to target excitatory transmission. A major limitation of this study is that it is restricted to an in vitro culture system, which makes it difficult to assess the full impact of *NLGN4* mutation on nervous system function. Nevertheless, the divergence of neuroligin-4 expression and function revealed by this work is an important reminder that models of both mouse and (wo)man are needed to fully understand the genetic basis of ASD.

Highlighted Article

Marro SG, Chanda S, Yang N, Janas JA, Valperga G, Trotter J, Zhou B, Merrill S, Yousif I, Shelby H, Vogel H, Kalani MYS, Südhof TC, Wernig M.

Neuroligin-4 Regulates Excitatory Synaptic Transmission in Human Neurons.

Neuron. 2019 Aug 21;103(4):617-626.e6. doi: 10.1016/j.neuron.2019.05.043.

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[https://www.cell.com/neuron/pdf/S0896-6273\(19\)30496-9.pdf](https://www.cell.com/neuron/pdf/S0896-6273(19)30496-9.pdf)